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Dysregulated peripheral endocannabinoid system signaling is associated with cognitive deficits in first-episode psychosis

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ABSTRACT

Among etiological explanations for psychosis, several hypotheses involving alterations on the immune/inflammatory system have been proposed. The endocannabinoid system (ECS) is an endogenous neuroprotective, anti-inflammatory system that modulates cognitive processes. Its altered expression has been associated with psychotic disorders. 73 patients with a first episode of psychoses (FEP) and 67 healthy controls were recruited in 5 university centers in Spain. The protein expression of the main peripheral ECS components was determined in peripheral blood mononuclear cells. The cognition function was assessed following the MATRICS consensus. After controlling for potential confounding factors, working memory statistically correlated to the peripheral N-acyl phosphatidylethanolamine phospholipase expression ($p = 0.039$). The short-term verbal memory correlated to the Diacylglycerol lipase ($p = 0.043$) and the fatty acid amide hydrolase ($p = 0.026$) expression. Finally, attention measures correlated to the Monoacylglycerol lipase expression, by means of the CPT-II commissions ($p = 0.036$) and detectability ($p = 0.026$) scores. The ECS may regulate the activation of key mediators in immune and inflammatory responses that may be involved in the primary neuronal stress phenomenon that occurs from the onset of psychotic illness. This study points a relationship between the ECS and the cognitive function in early psychosis and suggests the use of some of the ECS elements as biomarkers and/or pharmacological targets for FEP.

1. Introduction

Among etiological explanations for psychosis, several hypotheses involving alterations on the immune/inflammatory innate system have been proposed at both peripheral and central nervous system (CNS) (for review see (Leza et al., 2015)). The endocannabinoid system (ECS) has been described as an endogenous neuroprotective, anti-inflammatory system activated in diverse

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[1] FLAMM-PEPs is a multicentric, collaborative and translational group within CIBERSAM aimed to study inflammatory pathways in psychosis, both as possible biomarkers and as possible new therapeutic targets, incorporated in the PEPs study, a Spanish research project in first-episode psychosis.

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neuropathological scenarios to restore homeostasis, reducing both neurodegenerative and inflammatory damage (Hillard et al., 2012).

Briefly, the ECS is composed of endogenous ligands such as anandamide (AEA) and 2-arachidonoylglycerol (2AG); their cannabinoid G protein-coupled receptors, namely CB1 and CB2; the two main synthesis enzymes N-acyl phosphatidylethanolamine phospholipase (NAPE) and Diacylglycerol lipase (DAGL); and the enzymes fatty acid amide hydrolase (FAAH) and Monoacylglycerol lipase (MAGL) that are responsible for their degradation or reuptake.

Several studies have associated ECS alterations to psychotic disorders (for review, see (Zamberletti et al., 2012)). Our group described a peripheral endocannabinoid dysregulation in first-episode psychosis (FEP), with a significantly reduced expression of the endocannabinoid synthesis enzymes and an increased expression of the degradative ones (Bioque et al., 2013). Previously, cerebrospinal fluid (CSF) AEA levels were found elevated in subjects with acute schizophrenia (Giuffrida et al., 2004). Psychotic symptom remission has been associated to a significant decrease of the levels of AEA and to significant decrease in CB2 mRNA transcripts in peripheral blood mononuclear cells (PBMC) (De Marchi et al., 2003). The antipsychotic effect of cannabidiol has also been related to the inhibition of AEA deactivation (Leweke et al., 2012). A study in human postmortem brain tissues and cultured cells showed that genetically predetermined lower functioning of CB2 receptors (polymorphism Q63R) was related to an increased risk of schizophrenia when combined with other risk factors (Ishiguro et al., 2010). Postmortem studies have shown specific alterations in the levels of some endocannabinoids in different brain regions (Muguruza et al., 2013). Neuroimaging and PET studies show a reduced CB1 expression and activity in different brain areas of patients with schizophrenia (Eggan et al., 2008; Wong et al., 2011), while a greater CB1 availability may contribute to the increased susceptibility of schizophrenia subjects to the deleterious effects of cannabis use (Volk et al., 2014).

Besides, preclinical data demonstrate that ECS signaling is an important stress buffer that modulates emotional and cognitive functions, including learning and memory processes (Hillard et al., 2012; Pan et al., 2011), both in animal models and human subjects (Morena and Campolongo, 2014). Several studies in various neuroinflammatory diseases have described ECS alterations both in the central nervous system and in PBMC, leading some authors to suggest that peripheral endocannabinoid concentrations in the circulation and brain may be in equilibrium (Centonze et al., 2008; Hillard et al., 2012). However this assertion is controversial according to the evidence reported so far, particularly with AEA levels (Giuffrida et al., 2004; Koethe et al., 2009).

On the other hand, cannabis use is one of the most frequent and studied environmental risk factors related to psychosis (Matheson et al., 2011), though the neurobiological mechanisms underlying this increased susceptibility are poorly understood (see review in (Gage et al., 2015)). Around one third of FEP patients use cannabis (Myles et al., 2015), and its use in youth increases the risk of developing psychosis, with an estimated odds ratio of 2.10–2.93 (Torrey et al., 2012). Frequent cannabis exposure may down-regulate AEA signaling in patients with schizophrenia, but not in healthy individuals (Leweke et al., 2007).

It has also been described that patients in an early phase of schizophrenia or schizoaffective disorder who are carriers of the rs12720071 SNP G-allele may show an increased vulnerability to present certain difficulties on problem solving skills associated with altered brain areas rich in CB1 receptors when using cannabis (Ho et al., 2011).

A recent meta-analysis showed that patients with schizophrenia or FEP with a history of cannabis use have superior neuropsychological functioning compared with non-using patients, but the impact of cannabis use in cognitive performance of psychotic patients remains controversial (Sánchez-Torres et al., 2013; Yücel et al., 2012). The ECS may mediate in the effect of cannabis use in cognitive function, at least in some subjects (Vigano et al., 2009).

Based on these data, we hypothesized that altered peripheral ECS signaling may be associated with specific cognitive deficits in subjects in an early phase of a psychotic disorder. Controlling the main confounding factors, we aimed to study the relationship between a standardized neuropsychological battery performance and the protein expression of the main ECS components in PBMC samples from FEP patients and matched healthy controls, taking advantage of the PEPs project, a Spanish multicenter, case–control, longitudinal, naturalistic study (Bernardo et al., 2013).

2. Subjects and methods

2.1. Subjects

73 patients with a FEP and 67 matched healthy controls were recruited in five Spanish university centers, from September 2010 to April 2011. The inclusion criteria for patients were: age between 7 and 35 years, presence of the FEP in the last 12 months and speak Spanish correctly. The exclusion criteria for patients were: (1) mental retardation according to DSM-IV criteria (American Psychiatric Association (Washington), 1994), (2) history of head trauma with loss of consciousness and (3) presence of an organic disease with mental repercussions. Healthy controls were matched by age (±10%), gender and parental socio-economic status (SES), measured by the Hollingshead–Redlich scale (±1 level), and speak Spanish correctly. Their exclusion criteria were: (1), (2), (3), antecedent of psychotic or major affective disorder and having a first degree relative with psychotic disorder history.

The study was approved by the investigation ethics committees of all centers. Informed consent was obtained from all participants or from parents or legal guardians in under-age subjects. The rationale behind these criteria and the complete clinical protocol used in the PEPs project were previously published (Bernardo et al., 2013; Cuesta et al., 2015).

From the clinical groups that had collected the biological sample previously used to report a peripheral dysregulation of the ECS in FEP (Bioque et al., 2013) only those which had administered the neurocognitive battery to the subjects were included in this study.

2.2. Clinical assessment

The diagnosis was established by the semi-structured diagnostic interviews following the DSM-IV criteria (American Psychiatric Association (Washington), 1994). Apart from the interviews with each patient, multiple sources of information, including medical records and interviews with relatives, were used to establish the onset of positive psychotic symptoms (defined by scoring four or more at the PANSS scale items P1, P3, P5, P6 or G9, during the first week) and drug history (Bernardo et al., 2013; Kay et al., 1987). Following the international consensus (Gardner et al., 2010), the chlorpromazine potency equivalents of every antipsychotic doses were calculated. Clinical evaluation included a complete medical history, physical examination, laboratory tests and body mass index (BMI = weight in kg/height in m^2). Tobacco and cannabis use were evaluated using the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropAsi) (Kokkevi and Hartgers, 1995), considering the years of cannabis abuse or dependence following the DSM-IV criteria (American Psychiatric Association (Washington), 1994). A